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REMARKS

Status of the Claims

Claims 1, 28, 43, 44, 71, 86, 107, and 108 stand rejected under 35 U.S.C § 112, first paragraph, for failing to provide enablement for the terms "neoplasia disorder" and "preventing in a mammal."

Claims 1 and 44 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of co-pending Application No. 09/843,132 and No. 10/150,546.

Claim 109 stands rejected under 35 U.S.C § 112 for repeating Claim 87.

Claims 1-3, 11, 21, 43-46, 54, 71, 86-87, and 107-109 stand rejected under 35 U.S.C § 103(a) as being unpatentable over Karameris et al (Am. J. Respir. Crit Care Med 1997 December;156(6):1930-6) taken with Bunn et al (Semin Oncol 1994 Jun;21(3 Suppl. 6):49-59).

Rejection under 35 U.S.C § 112, first paragraph, for failing to provide enablement.

Treatment for Neoplasia Disorders

Claims 1, 28, 43, 44, 71, 86, 107, and 108 stand rejected under 35 U.S.C § 112, first paragraph, for failing to provide enablement for the terms "neoplasia disorder" and "preventing in a mammal." While the facts of *In re Brana*, 51 F3d 1560 may differ from the present facts, the law of *In re Johnson,* 282 F.2d 370 and *In re Brana* still remain applicable. At the time of the effective filing date, December 23, 1998, it was know to those skilled in the art to use the matrix metalloproteinase (MMP) inhibitor, prinomastat (AG-3340), in the treatment of neoplasia disorders. In a press release dated June 17, 1998 (**Appendix A, attached**), it was reported that in a preclinical trial "administration of AG-3340 resulted in a dose-dependent decrease in tumor growth by up to 65% as compared to controls." The test for sufficiency of compliance with § 112 is what the application as a whole communicates to one skilled in the art. *In re Johnson,* 282

but what about prevention

F.2d at 371. The United States Court of Customs and Patent Appeals in *Johnson* further elaborated on this test:

> In some cases an applicant may, merely by naming his new instrument or material, indicate what its use is, as, for example, by saying he has invented a "match," "hammer," "paint," "adhesive," or "detergent." He may or may not have to go further in order to enable others to use the invention, depending on its nature and on how much those of ordinary skill in the art know. In other words, compliance with the law does not necessarily require specific recitations of use but may be inherent in description or may result from disclosure of a sufficient number of properties to make a use obvious; and where those of ordinary skill in the art will know how to use, the applicant has a right to rely on such knowledge. If it will not be sufficient to enable them to use his invention, he must supply the know-how. *In re Johnson,* 282 F.2d at 371-2.

Taking into consideration the prior art previously mentioned and the disclosure of the specification, there is sufficient information to enable one skilled in the art to use the MMP inhibitor, AG-3340, for the treatment in neoplasia disorders.

In addition, topotecan and irinotecan were both commercially available at the time of the effective filing date. Both are recognized as treatments for neoplasia disorders. See **Appendix B, attached**.

See

According to *Miller Keane Encyclopedia & Dictionary of Medicine, Nursing & Allied Health* (6th ed.), the term "neoplastic" means pertaining to neoplasia or neoplasm. The term "neoplasm" means tumor; any new and abnormal growth, specifically one in which cell multiplication is uncontrolled and progressive. Ag-3340, irinotecan and topotecan are known to those skilled in the art for use in the treatment of neoplastic disorders and tumors. While some have been found specifically useful for certain types of tumors, it was not known for which types of tumors it is not useful for in treatment. To limit the claims to include only those types of tumors that are know to be benefited by these agents would be contrary to the "incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." *In re Brana* at 1568. *In re Brana* further provides "usefulness in patent law, and in particular the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." See *id.*

The Court has also recognized that "particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts." *In re Angstadt*, 537 F.2d 498, 503; 190 USPQ 214, 219 (CCPA 1976). The Court added "to require disclosures in patent applications to transcend the level of knowledge of those skilled in the art would stifle the disclosure of inventions in fields man understands imperfectly," See *id.* Since such limitations to certain types of neoplasia would require Applicant to transcend the level of knowledge of those skilled in the art, it is respectfully requests that the rejection be withdrawn.

Mode of Administration

It is know to one skilled in the art that the anti-neoplastic agents, campthothecins (irinotecan and topotecan) are administered intravenously. It is also know to one skilled in the are that the MMP inhibitor AG-3340 is administered orally. The specification on page 20 provides for a "combination therapy" wherein, "the therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally." Relying on the test used by the *In re Johnson* Court, there is sufficient information to provide enablement for purposes of § 112. Applicant respectfully requests withdrawal of this rejection.

Rejection under the judicially created doctrine of obviousness-type double patenting.

Claims 1 and 44 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of co-pending Application No. 09/843,132 and No. 10/150,546. Please find enclosed a Provisional Terminal Disclaimer in accordance with 37 C.F.R. § 1.321. Without acquiescing to the propriety of this rejection, applicants submit herewith a provisional terminal disclaimer, which is believed sufficient to obviate this rejection

Rejection under 35 U.S.C § 112

Claim 109 stands rejected under 35 U.S.C § 112, because it is a duplicate of Claim 87. Claim 109 had been canceled therefore the rejection is respectfully traversed.

Rejection under 35 U.S.C § 103(a) obviousness.

Claims 1-3, 11, 21, 43-46, 54, 71, 86-87, and 107-109 stand rejected under 35 U.S.C § 103(a) as being unpatentable over Karameris et al (Am. J. Respir. Crit Care Med 1997 December; 156(6):1930-6) taken with Bunn et al (Semin Oncol 1994 Jun;21(3 Suppl. 6):49-59).

The Karameris reference suggests that there is some "prognostic and therapeutic implications" that MMP inhibitors are useful in the treatment of squamous-cell lung cancer. The Bunn reference reports that irinotecan and topotecan have been used in combination with chemotherapy for the treatment of non-small cell lung cancer. While both references teach treatments for types of lung cancer there is no motivation to one skilled in the art to combine the two references.

It is well established that "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP 2143.01; *In re* Mills, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990).

The camptothecians (irinotecan and topotecan), are just one type of anti-neoplastic agent used in the treatment of lung cancer. For example, other types of anti-neoplastic agents include, but are not limited to, nitrogen mustards, folic acid analogs, vinca alkaloids, taxanes, epipodophyllotoxins, antibiotics and platinum coordination complexes. See Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed. The Bunn reference provides no motivation to select the camptothecian agents over the other agents that are known by one skilled in the art in the treatment of lung cancer. Further, no reference of record suggests the desirability of combining a MMP inhibitor with a camptothecian agent, specifically irinotecan or topotecan. Applicants respectfully request withdrawal of this rejection.

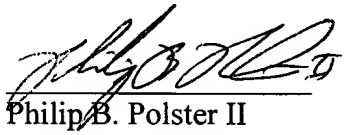
Conclusion

Claim 109 has been canceled. For all of the foregoing reasons, it is believed that the amended claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, she is cordially invited to contact Applicant's representative at the below listed number.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R 1.16 or 1.17 to Deposit Account No. **19-1025**.

Respectfully submitted,



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APPENDIX A

Reference number RF289688

Phase I data presented on Agouron's oral anti-angiogenesis drug AG-3340 in patients with advanced cancer; AG-3340 exhibits marked anti-tumor activity in preclinical models

Agouron Pharmaceuticals Inc

PRESS RELEASE 1998, June 17

Abstract

Agouron Pharmaceuticals Inc today released encouraging results from two phase I studies and one preclinical study of its oral anti-angiogenesis drug, AG-3340. The data were reported today at the 10th European Organization for Research and Treatment of Cancer (EORTC) meeting in Amsterdam, the Netherlands.

Phase I studies in advanced cancer patients

In a phase I safety and tolerability study of AG-3340 administered orally twice daily (BID) in patients with advanced cancer, including lung, prostate, kidney, and colorectal cancers as well as sarcoma and melanoma, disease was stabilized in more than 25% of 47 evaluable patients who were treated for periods of 16 to 40 weeks. Either two or three patients in each of five small dosing groups (5mg, 10mg, 25mg, 50mg and 100mg BID) comprising the 47 patients experienced stable disease. Three patients (one each with non-small cell lung cancer, renal carcinoma, and melanoma) were found to have minor reductions in tumor volume. Nine other evaluable patients in two additional dosing groups (1mg and 2mg BID) had not yet received 16 weeks of treatment and are still under evaluation. AG-3340 was found to be generally well tolerated in this study. Expected musculoskeletal side-effects, including arthralgias and body aches, occurred less frequently at doses below 25mg BID and were managed effectively by a rest from treatment followed by a dose reduction.

Based on the safety and tolerability data from this study, pivotal phase II/III clinical trials have been initiated using AG-3340 in 5mg, 10mg, and 15mg doses given BID in combination with standard chemotherapy in patients with advanced non-small cell lung cancer or advanced hormone-refractory prostate cancer.

AG-3340 is well tolerated in combination in advanced prostate cancer study

A separate phase I study found that AG-3340 in combination with chemotherapy was generally well tolerated among patients with advanced prostate cancer who were resistant to hormonal therapies. This study evaluated the use of AG-3340, in a dose of 25 mg BID, in combination with Novantrone (mitoxantrone) plus prednisone in 15 patients with advanced prostate cancer. In this ongoing study, nine patients have received the combination treatment for more than ten weeks; seven patients have received treatment for more than 18 weeks.

Pharmacokinetic analysis of the available data confirmed that AG-3340 blood levels are not affected by administration with mitoxantrone. No unexpected side-effects occurred in the patients in this study.

AG-3340 inhibits tumor growth in preclinical study

In a separate preclinical study, AG-3340 was found to be a potent inhibitor of the growth of chemotherapy-resistant human non-small cell lung cancer tumors in mice. Here, administration of AG-3340 resulted in a dose-dependent decrease in tumor growth by up to 65% as compared to controls. Paraplatin (carboplatin), a currently available chemotherapeutic agent, demonstrated a similar amount of anti-tumor effect at toxic doses, whereas AG-3340 inhibited growth at well-tolerated doses. The study also demonstrated that the combination of carboplatin

and AG-3340 was more effective than either agent alone, suggesting that the combination of the two drugs could provide beneficial clinical results.

A key action of AG-3340 was also demonstrated by finding a 77% reduction in the formation of new tumor-associated blood vessels. Neovascularization, or new blood vessel formation (angiogenesis), is required to support growing tumors. In animal studies, AG-3340 exerts anti-angiogenic effects, halting the formation of new blood vessels, and thereby starving tumor cells.

AG-3340 is an orally active, synthetic molecule designed to inhibit the growth, invasion and metastasis of solid tumors by inactivating certain members of a family of enzymes known as matrix metalloproteases (MMPs). AG-3340 selectively inhibits those MMPs believed to be involved in tumor progression. A primary goal of the clinical studies of AG-3340 is to determine whether this distinctive selectivity results in a favorable clinical profile of safety and efficacy. Agouron is also conducting preclinical evaluations of third-generation MMP inhibitors with selectivity profiles distinct from that of AG-3340.

The reference is cited in the following reports

prinomastat. *Updated on 10th June 2002.* Originator: Pfizer Inc

APPENDIX B

Oncology Tools

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

FDA Oncology Tools Approval Summary for topotecan for Treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

Generic Drug Name	topotecan
Trade Name	Hycamtin
Sponsor or Applicant	GlaxoSmithKline
Application Number	020671
Supplement Number	000
Supplement Type Code	N
Dosage Form	intravenous injection
General Indication	ovary
Line or type of therapy	Second
Specific Indication	Treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.
Subpart H-Accelerated Approval?	0
Filing Date	Dec 21 1995
Advisory Committee Date	Apr 19 1996
Advisory Committee Recommendation	Approve: 8 yes, 0 no
Approval Date	May 28 1996
Number of Studies Reviewed	2
Study Comments	Study 039 compared topotecan (n=112) to paclitaxel (n=114) in patients with recurrent metastatic ovarian cancer after a platinum-containing regimen. This study allowed for crossover of patients who did not respond to treatment on the initial arm of the trial. Study 034 was an open-label, non-comparative trial in 111 patients with recurrent ovarian cancer after treatment with a platinum-containing regimen.
Study Results	See individual studies. Survival results are incomplete (majority of patients were still alive at the time of study closure, June 1995) and will be provided as part of a Phase IV commitment. In the crossover phase of Study 039, 9.4% (5/53) of patients who received topotecan after paclitaxel had a partial response and 2.7% (1/37) of patients who received paclitaxel after topotecan had a complete response.
Study Details (Click on NDA or Supplement Number to view details)	NDA 020671 Supplement 000
Follow Up Commitments	-Provide updated survival and other efficacy data for studies 39, 34, and 33. -DMF holder to provide English translation of the master production record. -Annual stability study of future batches of drug substance under long-term storage conditions.

Postmarketing Reports of Adverse Events. Reports of adverse events in patients taking Hycamtin (topotecan hydrochloride) received after market introduction, which are not listed above, include the following:

Hematologic: *Rare* -- severe bleeding (in association with thrombocytopenia).

Skin/Appendages: *Rare* -- severe dermatitis, severe pruritus.

Body as a Whole: *Infrequent* -- allergic manifestations; *rare* -- anaphylactoid reactions, angioedema.

OVERDOSAGE

There is no known antidote for overdosage with *Hycamtin* . The primary anticipated complication of overdosage would consist of bone marrow suppression.

One patient on a single-dose regimen of 17.5 mg/m ^{2} given on day 1 of a 21-day cycle had received a single dose of 35 mg/m ^{2} . This patient experienced severe neutropenia (nadir of 320/mm ^{3}) 14 days later but recovered without incident.

The LD_{10} in mice receiving single intravenous infusions of *Hycamtin* was 75 mg/m ^{2} (CI 95%: 47 to 97).

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of *Hycamtin* , patients must have a baseline neutrophil count of >1500 cells/mm ^{3} and a platelet count of >100,000 cells/mm ^{3} . The recommended dose of Hycamtin (topotecan hydrochloride) is 1.5 mg/m ^{2} by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. In the absence of tumor progression, a minimum of four courses is recommended because tumor response may be delayed. The median time to response in three ovarian clinical trials was 9 to 12 weeks and median time to response in four small cell lung cancer trials was 5 to 7 weeks. In the event of severe neutropenia during any course, the dose should be reduced by 0.25 mg/m ^{2} for subsequent courses. Doses should be similarly reduced if the platelet count falls below 25,000 cells/mm ^{3} . Alternatively, in the event of severe neutropenia, G-CSF may be administered following the subsequent course (before resorting to dose reduction) starting from day 6 of the course (24 hours after completion of topotecan administration).

Adjustment of Dose in Special Populations

Hepatic Impairment: No dosage adjustment appears to be required for treating patients with impaired hepatic function (plasma bilirubin >1.5 to <10 mg/dL).

Renal Functional Impairment: No dosage adjustment appears to be required for treating patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min.). Dosage adjustment to 0.75 mg/m ^{2} is recommended for patients with moderate renal impairment (20 to 39 mL/min.). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

Elderly Patients: No dosage adjustment appears to be needed in the elderly, other than adjustments related to renal function.

PREPARATION FOR ADMINISTRATION

Precautions: *Hycamtin* is a cytotoxic anticancer drug. As with other potentially toxic compounds, *Hycamtin* should be prepared under a vertical laminar flow hood while wearing gloves and protective clothing. If *Hycamtin* solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If *Hycamtin* contacts mucous membranes, flush thoroughly with water.

Preparation for Intravenous Administration: Each *Hycamtin* 4 mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of Hycamtin (topotecan hydrochloride) are stable until the date indicated on the package when stored between 20° and 25°C (68° and 77°F) [see USP] and protected from light in the original package. Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of *Hycamtin* diluted for infusion are stable at approximately 20° to 25°C (68° to 77°F) and ambient lighting conditions for 24 hours.

HOW SUPPLIED

Hycamtin (topotecan hydrochloride) for Injection is supplied in 4 mg (free base) single-dose vials.

NDC 0007-4201-01 (package of 1)

NDC 0007-4201-05 (package of 5)

Storage: Store the vials protected from light in the original cartons at controlled room temperature between 20° and 25°C (68° and 77°F) [see USP].

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published. [1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT PHOTO(S):

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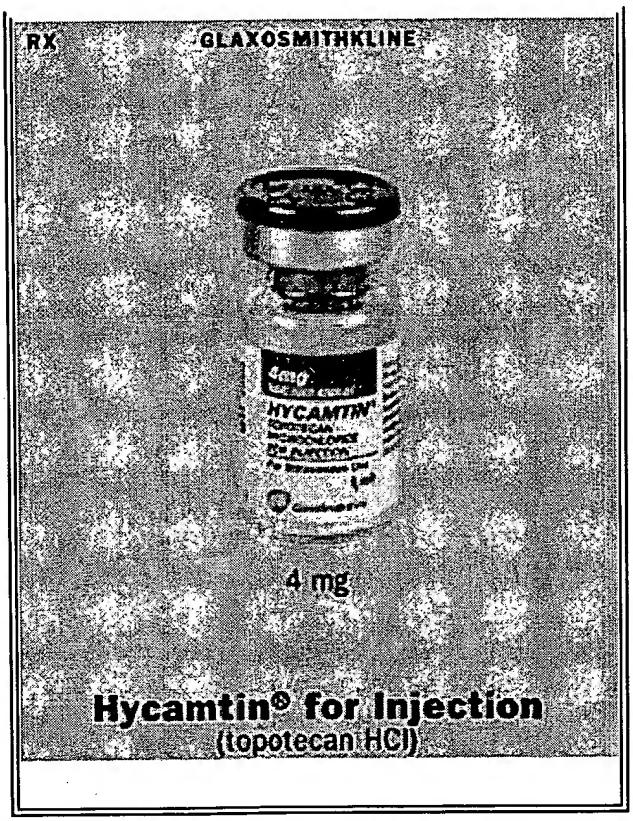
The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.



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2. AMA Council Report. Guidelines for handling parenteral antineoplastics. *JAMA.* 1985;253 (11):1590-1592.
3. National Study Commission on Cytotoxic Exposure-recommendations for handling cytotoxic agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
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5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* . 1983;Sept./Oct.:258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* . 1990;47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm* . 1996;53:1669-1685.

GlaxoSmithKline, Research Triangle Park, NC 27709

November 2001/HY:L12

U.S. Food and Drug Administration • Center for Drug Evaluation and Research

FDA Oncology Tools Approval Summary for irinotecan for Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

Generic Drug Name	irinotecan
Trade Name	Camptosar
Sponsor or Applicant	Pharmacia & Upjohn Company
Application Number	020571
Supplement Number	000
Supplement Type Code	N
Dosage Form	intravenous injection
General Indication	colon-rectum
Line or type of therapy	Second
Specific Indication	Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.
Subpart H-Accelerated Approval?	1
Filing Date	Dec 28 1995
Advisory Committee Date	Jun 13 1996
Advisory Committee Recommendation	Accelerated Approval: 9 yes, 0 no
Advisory Committee Transcript	Hyperlink to Advisory Committee Transcript
Approval Date	Jun 14 1996
Number of Studies Reviewed	3
Study Comments	Data from three multicenter open-label, Phase 2, single-agent studies involving a total of 304 pts in 59 centers. Patients had metastatic colorectal cancer that recurred or progressed following 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effect on survival and disease related symptons.
Study Results	The studies show an overall response rate in 12.8% (95% CI: 9.1%-16.6%) of patients (39 of 304 patients; 0.7% CR, 12.2% PR). Among the 193 patients treated at the 125 mg/m2 starting dose, the overall response rate was 15.0% (2 CR , 27 PR; 95% CI: 10.0%, 20.1%). The median duration of response was 6 months (range: 2.6-15.1 months). The median duration of response for patients beginning therapy at 125 mg/m2 was 5.8 mo (range: 2.6-15.1 mo.). Dose limiting toxicities include severe delayed diarrhea and myelosuppression.

observed in patients receiving CAMPTOSAR; the specific cause of these events has not been determ

Other Non-U.S. Clinical Trials

Irinotecan has been studied in over 1100 patients in Japan. Patients in these studies had a variety c types, including cancer of the colon or rectum, and were treated with several different doses and sc In general, the types of toxicities observed were similar to those seen in U.S. trials with CAMPTOSAI some information from Japanese trials that patients with considerable ascites or pleural effusions we increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consi dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to because these patients also had lung tumors and some had preexisting nonmalignant pulmonary dis result of these observations, however, clinical studies in the United States have enrolled few patient compromised pulmonary function, significant ascites, or pleural effusions.

Post-Marketing Experience

The following events have been identified during postmarketing use of CAMPTOSAR in clinical practi of colitis complicated by ulceration, bleeding, ileus, or infection have been observed. There have bee cases of renal impairment and acute renal failure, generally in patients who became infected and/or depleted from severe gastrointestinal toxicities (see WARNINGS).

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have also been c (see WARNINGS).

OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m ^{2} of irinotecan were administered to patients various cancers. Single doses of up to 750 mg/m ^{2} of irinotecan have been given in non-U.S. trials. adverse events in these patients were similar to those reported with the recommended dosage and There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be inst prevent dehydration due to diarrhea and to treat any infectious complications.

DOSAGE AND ADMINISTRATION

Combination-Agent Dosage

Dosage Regimens

CAMPTOSAR Injection in Combination with 5-Fluorouracil (5-FU) and Leucovorin (LV)

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes (see Preparation of Solution). For all regimens, the dose of LV should be administered immediately after CAMPTOSAR, v administration of 5-FU to occur immediately after receipt of LV. CAMPTOSAR should be used as recommended; the currently recommended regimens are shown in Table 10.

Dosing for patients with bilirubin >2 mg/dL cannot be recommended since such patients were not ir clinical studies. It is recommended that patients receive premedication with antiemetic agents. Prop therapeutic administration of atropine should be considered in patients experiencing cholinergic sym See PRECAUTIONS , General .

Dose Modifications

Patients should be carefully monitored for toxicity and assessed prior to each treatment. Doses of CAMPTOSAR and 5-FU should be modified as necessary to accommodate individual patient tolerance treatment. Based on the recommended dose-levels described in Table 10, Combination-Agent Dosa Regimens & Dose Modifications, subsequent doses should be adjusted as suggested in Table 11, Recommended Dose Modifications for Combination Schedules. All dose modifications should be base worst preceding toxicity. After the first treatment, patients with active diarrhea should return to pre bowel function without requiring antidiarrhea medications for at least 24 hours before the next chen administration.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Trea may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient ha recovered, consideration should be given to discontinuing therapy. Provided intolerable toxicity does develop, treatment with additional cycles of CAMPTOSAR/5-FU/LV may be continued indefinitely as l patients continue to experience clinical benefit.

Table 10. Combination-Agent Dosage Regimens & Dose Modifications

Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR	125 mg/m ^{2} IV over 90 min, d 1,8,15,22		
	LV	20 mg/m ^{2} IV bolus, d 1,8,15,22		
5-FU	500 mg/m ^{2} IV bolus, d 1,8,15,22			
	Starting Dose & Modified Dose Levels (mg/m ^{2})			
	Starting Dose	Dose Level -1	Dose Level -2	
CAMPTOSAR	125	100	75	
LV	20	20	20	
5-FU	500	400	300	
Regimen 2 6-wk cycle with infusional 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR	180 mg/m ^{2} IV over 90 min, d 1,15,2		
	LV	200 mg/m ^{2} IV over 2 h, d 1,2,15,16,29,30		
	5-FU Bolus	400 mg/m ^{2} IV bolus, d 1,2,15,16,29,30		
	5-FU Infusion [b]	600 mg/m ^{2} IV over 22 h, d 1,2,15,16,29,30		
		Starting Dose & Modified Dose		

		Levels (mg/m ^{2})		
		Starting Dose	Dose Level -1	Dos Lev -2
	CAMPTOSAR	180	150	12
	LV	200	200	20
	5-FU Bolus	400	320	24
	5-FU Infusion [b]	600	480	36

[a] Dose reductions beyond dose level -2 by decrements of approximately 20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

[b] Infusion follows bolus administration.

Table 11. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to >/= 1500/mm ^{3}, and the platelet count has recovered to >/= 100,000/mm ^{3}, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

Toxicity NCI CTC Grade [a] (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy [b]**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm ^{3})	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm ^{3})	down 1 dose level	Maintain dose level
3 (500 to 999/mm ^{3})	Omit dose until resolved to </= grade 2, then down 1 dose level	down 1 dose level

4 (<500/mm ^{3})	Omit dose until resolved to </= grade 2, then down 2 dose levels	down 2 dose levels
Neutropenic fever	Omit dose until resolved, then down 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria a are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx [c])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then down 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then down 1 dose level	down 1 dose level
4 (>/=10 stools/day > pretx)	Omit dose until resolved to baseline, then down 2 dose levels	down 2 dose levels
Other nonhematologic toxicities [d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to </= grade 1, then down 1 dose level	Maintain dose level
3	Omit dose until resolved to </= grade 2, then down 1 dose level	down 1 dose level
4	Omit dose until resolved to </= grade 2, then down 2 dose levels	down 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR	*For mucositis/stomatit decrease only 5-FU, n CAMPTOSAR*
[a] National Cancer Institute Common Toxicity Criteria (version 1.0)		
[b] Relative to the starting dose used in the previous cycle		
[c] Pretreatment		
[d] Excludes alopecia, anorexia, asthenia		

Single-Agent Dosage Schedules

Dosage Regimens

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both the weekly once-every- 3-week dosage schedules (see Preparation of Infusion Solution). Single-agent dosage r are shown in Table 12.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients wi the following conditions: age >/=65 years, prior pelvic/abdominal radiotherapy, performance status increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended since patients were not included in clinical studies.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or thera administration of atropine should be considered in patients experiencing cholinergic symptoms. See PRECAUTIONS , General .

Dose Modifications

Patients should be carefully monitored for toxicity and doses of CAMPTOSAR should be modified as r to accommodate individual patient tolerance to treatment. Based on recommended dose-levels desc Table 12, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should adjusted as suggested in Table 13, Recommended Dose Modifications for Single-Agent Schedules. A modifications should be based on the worst preceding toxicity.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Trea may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient ha recovered, consideration should be given to discontinuing this combination therapy. Provided intoler toxicity does not develop, treatment with additional cycles of CAMPTOSAR may be continued indefin long as patients continue to experience clinical benefit.

Table 12. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Weekly Regimen [a]	125 mg/m ^{2} IV over 90 min, d 1,8,15,22 then 2-wk rest		
	Starting Dose & Modified Dose Levels [c] (mg/m ^{2})		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Once-Every-3-Week Regimen [b]	350 mg/m ^{2} IV over 90 min, once every 3 wks [c]		
	Starting Dose & Modified Dose Levels (mg/m ^{2})		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

[a] Subsequent doses may be adjusted as high as 150 mg/m ^{2} or to as low as 50 mg/m ^{2} in 25 to 50 mg/m ^{2} decrements depending upon individual patient tolerance.

[b] Subsequent doses may be adjusted as low as 200 mg/m ^{2} in 50 mg/m ^{2}

decrements depending upon individual patient tolerance.

[c] Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 13. Recommended Dose Modifications for Single-Agent Schedul

A new cycle of therapy should not begin until the granulocyte count has recovered to >/=1500/mm ^{3}, and the platelet count has recovered to >/=100,000/mm ^{3}, and treatment-related diarrhea is fully resolved. Trea should be delayed 1 to 2 weeks to allow for recovery from treatment-rela toxicities. If the patient has not recovered after a 2-week delay, consider should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade [b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cy of Therapy (After Adequat Recovery), Compared witl Starting Dose in the Previ Cycle [a]**	
	Weekly	Weekly	Once Eve Weeks
No toxicity	Maintain dose level	up 25 mg/m ^{2} up to a maximum dose of 150 mg/m ^{2}	Maintain level
Neutropenia			
1 (1500 to 1999/mm ^{3})	Maintain dose level	Maintain dose level	Maintain level
2 (1000 to 1499/mm ^{3})	down 25 mg/m ^{2}	Maintain dose level	Maintain level
3 (500 to 999/mm ^{3})	Omit dose until resolved to </= grade 2, then down 25 mg/m ^{2}	down 25 mg/m ^{2}	down 50 ^{2}
4 (<500/mm ^{3})	Omit dose until resolved to </= grade 2, then down 50 mg/m ^{2}	down 50 mg/m ^{2}	down 50 ^{2}
Neutropenic fever	Omit dose until resolved, then down 50 mg/m ^{2} when resolved	down 50 mg/m ^{2}	down 50 ^{2}
Other hematologic	Dose modifications for leukopenia, thrombocytopenia, and		

toxicities	anemia during a cycle of therapy and at the start of subse cycles of therapy are also based on NCI toxicity criteria ar the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretx [c])	Maintain dose level	Maintain dose level	Maintain level
2 (4-6 stools/day > pretx)	down 25 mg/m ^{2}	Maintain dose level	Maintain level
3 (7-9 stools/day > pretx)	Omit dose until resolved to </= grade 2, then down 25 mg/m ^{2}	down 25 mg/m ^{2}	down 50 ^{2}
4 (>/= 10 stools/day > pretx)	Omit dose until resolved to </= grade 2, then down 50 mg/m ^{2}	down 50 mg/m ^{2}	down 50 ^{2}
Other nonhematologic toxicities [d]			
1	Maintain dose level	Maintain dose level	Maintain level
2	down 25 mg/m ^{2}	down 25 mg/m ^{2}	down 50 ^{2}
3	Omit dose until resolved to </= grade 2, then down 25 mg/m ^{2}	down 25 mg/m ^{2}	down 50 ^{2}
4	Omit dose until resolved to </= grade 2, then down 50 mg/m ^{2}	down 50 mg/m ^{2}	down 50 ^{2}
[a] All dose modifications should be based on the worst preceding toxicity			
[b] National Cancer Institute Common Toxicity Criteria (version 1.0)			
[c] Pretreatment			
[d] Excludes alopecia, anorexia, asthenia			

Preparation & Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and prepa infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is recommended. If a solu CAMPTOSAR contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guide handling and disposal of anticancer agents are available. [1-7]

Preparation of Infusion Solution

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn fr into syringe.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrc Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range c 2.8 mg/mL. In most clinical trials, CAMPTOSAR was administered in 250 mL to 500 mL of 5% Dextr Injection, USP.

The solution is physically and chemically stable for up to 24 hours at room temperature (approximal and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and protected from light are physically and ch stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided. Because c microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dext Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures pr with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used w hours if kept at room temperature (15° to 30°C, 59° to 86°F).

Other drugs should not be added to the infusion solution. Parenteral drug products should be inspec visually for particulate matter and discoloration prior to administration whenever solution and conta permit.

HOW SUPPLIED

Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) w hydroxide or hydrochloric acid.

CAMPTOSAR Injection is available in single-dose amber glass vials in the following package sizes:

2 mL NDC 0009-7529-02

5 mL NDC 0009-7529-01

This is packaged in a backing/plastic blister to protect against inadvertent breakage and leakage. Th should be inspected for damage and visible signs of leaks before removing the backing/plastic bliste damaged, incinerate the unopened package.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommen the vial (and backing/plastic blister) should remain in the carton until the time of use.

Rx only

REFERENCES

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